UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,774	06/19/2000	Bernd Groner	4-19924C/C1C1	4601

26633 7590 07/09/2004

HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K STREET,NW
SUITE 300
WASHINGTON, DC 20006

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/596,774	GRONER ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1,8,12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-7,9-11,13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending. Claims 1, 8, 12 and 14 remain withdrawn from consideration. Claims 2-7, 9-11, 13 and 15 are under consideration.

2. The objection to the specification for the incorporation of essential material in the specification on page 5, lines 4-6, by reference to a foreign application or patent is maintained. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Applicant argues that the material incorporated by reference has been known to the skilled artisans for 10 years, and that adding further information already known is not needed to practice the invention under these circumstances. This has been considered but not found persuasive. If said material is already known to the skilled artisan for 10 years then applicant is invited to delete the statement that said material is "incorporated by reference" in order to overcome the objection to the specification.

3. The rejection of claims 2-7, 9-11, 13 and 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the following reasons of record.

The metes and bounds of claims 2 and 5 cannot be determined because the difference between a "functional" zeta chain of a TCR and "the" zeta chain of the TCR is not set forth in the specification.

Claim 2 is rendered vague and indefinite in the recitation of "derivable" from an anti-ErbB2 antibody" and "derivable" from the T-cell receptor. The recitation of "derivable from" rather than "derived from" indicates that the claimed antigen binding domains and zeta chains are not absolutely limited to the antigen binding domains of the anti-Erb2 antibody or the zeta chain

of the TCR, as "derivable from" can read on structural alterations of said antigen binding domain and zeta chain.

Applicant argues that the function of the zeta chain is described throughout the specification. this has been considered but not found persuasive. The functions of the zeta chain as discussed in the specification are preferred embodiments of zeta chain function and do not constitute a limitation regarding the metes and bounds of a functional zeta chain as claimed. Applicant is advised to delete "functional" from claim 2.

Applicant argues that one of skill in the art would understand that the term "derivable" can indeed read on structural alterations of said antigen binding domain and zeta chain, and because skill in the art is high, use of the term "derivable" is not vague and indefinite. This has been considered but not found persuasive. The rejection of the term "derivable" is under 112, second paragraph, for lacking definite metes and bound, not under 112, first paragraph for lacking enablement. Accordingly, the relative skill in the art is not an issue here but whether the metes and bounds of the claim is exactly defined.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks deposit information for the monocloanl antibodies. .One of skill in the art must know how to make and use the claimed monoclonal antibodies and it is not clear if the exact cell line producing the antibodies can be made without undue experimentation.

Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue

experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibodies described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice..

5. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 10 has been amended to incorporate the limitation "removing bifunctional protein from the host cell culture". The specification as filed described leader sequences for the targeting of the recombinant protein to the membrane of the host cell (page 12, lines 16-20). this is insufficient support for a method of producing a protein comprising expressing said protein and removing the bifunctional protein from the host cell culture which would require the secretion of said protein which is contrary to the insertion of the protein in the membrane..

6. The rejection of claims 2, 4-7, 9-11, and 15 under 35 U.S.C. 103(a) as being unpatentable over Capon et al (WO 92/10591, reference AC of the IDS filed Sep 19, 2000) in view of Wels et al (EP 502,812, reference AP of the IDS filed Sep 19, 2000) and Huse et al (Science, 1989, Vol. 246, pp. 1275-1281) is maintained for reasons of record. Claim 13 is also rejected for the same reasons of record.

Claim 2 is drawn to a DNA encoding a bifunctional protein, wherein said protein comprises: (i) an antigen-binding domain derivable from an anti-ErbB2 antibody; (ii) a hinge region comprising from about 40 to about 200 amino acids, and (iii) a functional zeta chain derivable for the T-cell antigen receptor wherein the hinge region couples the antigen binding

domain to the functional zeta chain. Claim 4 embodies the DNA of claim 2 wherein the hinge region is an immunoglobulin-hinge region.

Claim 5 embodies the DNA of claim 2 wherein the functional zeta chain comprises the transmembrane and cytoplasmic domain of the zeta chain. Claim 6 is drawn to a host cell expressing the DNA of claim 2. Claim 7 embodies the host cell of claim 6 wherein said host cell is a cytotoxic lymphocyte. Claim 11 is drawn to a composition comprising the host cell of claim 6. Claim 15 is drawn to a vector comprising the DNA of claim 2.

Claim 9 is drawn to a process of endowing a CTL with a MHC-independent and unrestricted tumor cell specificity comprising introducing the DNA of claim 2 into a CTL.

Claim 10 is drawn to a method for producing a bifunctional protein comprising the protein culturing a host cell comprising the DNA encoding said protein under conditions which allow the expression of a protein under conditions which allow the expression of a protein encoded by the DNA of claim 2 and removing the bifunctional protein from the host cell culture.

Capon et al teach the DNA encoding a chimeric protein comprising and extracellular domain capable of binding to a ligand and transmembrane domain and a cytoplasmic domain capable of activating a signaling pathway. Capon et al teach the zeta chain of the T-cell receptor as the cytoplasmic domain (page 5, lines 16-17 and claim 11). Capon et al teach that the transmembrane domain may be the domain of the protein contributing the cytoplasmic portion (page 6, lines 26-27, and claim 7), thus fulfilling the specific embodiment of claim 5 drawn to the transmembrane and cytoplasmic domains of the zeta chain. Capon et al teach that the extracellular domain may be part of a protein which is monomeric, homodimeric, heterodimeic or associated with a larger number of proteins and in particular may consist of an Ig heavy chain which may in turn be covalently associated with the Ig light chain by virtue of the presence of CH1 and hinge regions or may become covalently associated with other Ig heavy/light chain complexes by virtue of the presence of hinge, CH2 and CH3 domains (page 7, lines 18-27, and claims 3 ,12 and 17-19). Claim 47 of Capon et al states that a binding site is defined by the mammalian cell expressing the extracellular domain bound to a second protein, which is consistent with the association of the Ig heavy chain with the Ig light chain by means of the hinge region. It is recognized that the binding site of an antibody is formed by association of the CDR from the light chain and the CDR from the heavy chain. Capon et al teach that for the

antibody receptor, ligands of interest include the Her-2 protein which is amplified in human breast and ovarian carcinomas (page 16, lines 16-21). Capon et al teach an expression cassette comprising the DNA encoding the chimeric protein (claim 8) and a cytotoxic T-lymphocyte as a host cell (claims 24 and 25), thus fulfilling the limitation of claim 7. Capon et al teach the cytotoxic lymphocyte comprising the chimeric protein wherein said cell is substantially free of Class I or Class II MHC (claim 26) and a method for activating cells comprising contacting said cells with a ligand which binds to said extracellular domain and transduces a signal to said cytoplasmic domain , thus fulfilling the specific embodiment of claim 9. Capon et al teach a method of producing the chimeric protein by means of transformation and culturing of a host cell by means o an expression cassette which results in the secretion of the product (page 15, lines 1-4) fulfilling the limitations of claim 10.

Capon et al, although suggesting a target ligand of Her-2 for a method of treating cancer, does not specifically teach DNA encoding a chimeric protein wherein the extracellular portion comprises an antigen-binding domain derivable from an anti-ErbB2 antibody.

Wels et al teach the cDNA encoding chimeric proteins comprising an antigen-biding domain derivable for an anti-ErbB2 antibody, wherein the portion of the DNA encoding the antigen-binding domain comprises the scFv of FRP5 which is taught by Wels et al to be SEQ ID NO:4 (page 31). Wels et al teach that SEQ ID NO:1 was the variable heavy chain of the anti-ErbB2 antibody and SEQ ID NO:2 was the variable light chain of said antibody (page 20, lines 31-32).

Huse et al teach that monovalent Fab fragments have less affinity for antigen than bivalent antibodies (page 1280, second column, lines 3-5 of the second full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the DNA encoding the light chain variable region and the DNA encoding the heavy chain variable region as the extracellular domains in the method taught by Capon et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Wels et al on the ability of the recombinant fusion proteins comprising said DNA to bind exhibit the characteristic of the anti-ErbB2 antibody in binding to target antigen, and the teachings of Capon et al who suggest that the extracellular domain of the fusion proteins be a ligand for the Her-2 protein which is

synonymous with ErbB2. One of skill in the art would be motivated to express the chimeric protein comprising the cytoplasmic domain and the transmembrane domain of the zeta chain of the T-cell receptor fused to the single chain antibody of the anti-ErbB2 antibody in addition to an immunoglobulin hinge region so as expression of the chimeric protein in lymphocytes allowed for the formation of dimers of said chimeric proteins by virtue of the cysteine residues within the transmembrane region of the zeta chain, known to comprise a cysteine residue capable of disulfide bonding (Capon et al, page 7, lines 5-7) and by virtue of the hinge region of the antibody (Capon et al, page 7, lines 21-27). One of skill in the art would be motivated to form extracellular regions comprising dimers of the single chained antibody because the resulting dimeric protein would be bivalent and be expected to have a greater affinity for antigen than the monomeric single chained recombinant antibody.

7. Applicant argues that the teaching of Huse et al regarding the decreased affinity of Fab fragments for antigen relative to bivalent antibodies having both heavy and light chains does not apply to the non-analogous materials recited in the claims. This has been considered but not found at all persuasive. The materials in the claims encompass an antigen binding domain from a anti-ErbB2 antibody. Both Huse et al and the instant claims are concerned with antigen binding domains. Thus the application of the teachings of Huse et al regarding the affinity of a Fab fragment to the instant claims is not non-analogous art.

Applicant agues that the hinge region in the instant claims serves as a positioner allowing the extracellular ligand binding domain to protrude a certain distance range from the host cell, and is not used, as the examiner contends as a means of attaching the light chain of an antibody. This has been considered but not found persuasive. The motivation to include the hinge region as a means of attaching an antibody light chain renders the instant claims obvious. It is not necessary to combine references to render an invention obvious for the same reasons as applicant, because a product is obvious over the prior art as long as there is motivation to combine the teachings of the prior art. It is not required that the motivation be identical to that relied upon by applicant.

Applicant further argues that the zeta chain of the receptor always exists as a dimer due to disulfide bridge formation between the extracellular cysteines and therefore the zeta chain

would have been expected to exist as a dimer. This has been considered but not found persuasive. The dimer formed by the zeta chain would be joined to the same antigen binding domain of the anti-ErbB2 antibody and would not form a divalent antibody with increased binding affinity.

Applicant argues that according to page 7, lines 18-27 of Capon the hinge region is an internal portion within the extracellular domain of Capon. this has been considered but not found to be persuasive. Capon states that "Depending on the function of the antibody, the desired structure and the signal transduction the entire chain may be used or a truncated chain may be used, where all or part of the CH1, CH2 or CH3 domains may be removed or all or part of the hinge region may be removed. Various naturally occurring receptors may also be employed, wherein the receptors, such as CD4, CD8-alpha, or cytokine or hormone receptors. The receptor may be responsive to a natural ligand, an antibody or a fragment thereof, a synthetic molecule, e.g. drug, or any other agent which is capable of inducing a signal". Thus, Capon clearly teaches that the domains of the antibody can be separated and removed as needed. One of skill in the art would clearly see that a truncated heavy chain can be used because the Fc portion of the heavy chain would not be needed to transmit a signal (page 9, lines 4-5). Capon teaches that the light an heavy regions may be fused together to form a variable region (page 9, lines 5-6). This is consistent with the formation of a bivalent antibody binding region through attachment of a light chain to the heavy chain by means of the hinge region.

Applicant again argues that Capon does not teach a hinge region of 40-200 amino acids and to the extent that any hinge region exists in Capon it is merely part of an extracellular domain. this has been considered but not found persuasive. the claims do not contain limitations that would exclude the hinge region being part of a natural antibody hinge region in the extracellular domain.

Applicant points out that the above arguments are "backed up by real world experience". and that a construct lacking a hinge region would be non-functional and therefore not meet the claim limitations. This has been considered but not found persuasive. Stancovski et al (Journal of Immunology, 1993, Vol. 11, pp. 6577-6582, cited in a previous Office action) teaches an anti-Her-2 antibody extracellular portion fused to the zeta chain of the T-cell receptor which

functions to bind to Her-2 and activate the T-cell. The disclosure of Stancovski does not include a linker region.

8. Claims 6, 7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using host cells comprising the DNA of claim 2 in vitro or ex vivo, and a method of endowing CTL with a MHC-independent and unrestricted tumor cell specificity comprising introducing the DNA of claim 2 into the T-cell in vitro or ex-vivo, does not reasonably provide enablement for host cells comprising the DNA of claim 2 made by gene therapy means and a method for making CTL having a MHC-independent and unrestricted tumor cell specificity comprising introducing the DNA of claim 2 into the T-cell by gene therapy means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 6 and 7 are drawn to "host cell" comprising the DNA of claims 2. Claim 9 is drawn to a process of endowing CTL with a MHC-independent and unrestricted tumor cell specificity comprising introducing the DNA of claim 2 into the T-cell. The specification contemplates both the transduction of T-cells in vitro of ex-vivo, as well as the administration of the of DNA directly into a mammal in need of cancer treatment (page 15, lines 12-13). The specification is not enabling for said in vivo process or the host cells obtained thereby for the following reasons:.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken

up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type of T-cells, nor does the specification does not teach how to target exogenous nucleic acids selectively into T-cells.

Clearly, the specification fails to describe a method of transferring the DNA of the instant claims into a patient which would result in a CTL with a defined MHC independent and unrestricted tumor specificity which would be therapeutic for the treatment of cancer. Without specific guidance as to how to overcome the unreliability of the gene therapy art, one of skill in the art would be subject to undue experimentation in order to carry out said method .

9. All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
06/01/2004

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER